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By: Judith Muzyk Date: November 25, 2003
Judith Muzyk

Docket No.: 242/9-1568

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Roberto Valducci		
Serial No.:	09/898,425	Group Art Unit: 1615	
Filing Date:	July 3, 2001	Examiner: Blessing M. Fubara	
For:	ORAL SOLID PHARMACEUTICAL FORMULATION WITH PH-DEPENDENT MULTIPHASIC RELEASE		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION OF TRANSLATION OF FOREIGN PRIORITY APPLICATION (37 CFR 1.55)

Sir:

In response to the Office Action of August 26, 2003, the applicant submits herewith an English translation of the certified priority document already of record, Italian Patent Application No. MI2000A001603, filed July 14, 2000. The undersigned hereby states that the translation of the certified copy is accurate.

Respectfully submitted,

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MINISTRY OF THE PRODUCTIVE OPERATIONS

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Authentication of a copy of documents relating to the Patent Application for:
INDUSTRIAL INVENTION
No MI2000 A 001603

It is certified that the accompanying copy is a true copy of the original documents filed with the Patent Application mentioned above, whose details appear in the attached filing certificate.

Rome, 30 August 2001

The Director
Ing. Giorgio ROMANI

Seal

TO MINISTRY OF THE INDUSTRY COMMERCE AND CRAFT **MODULE A**

ITALIAN PATENT AND TRADEMARK OFFICE - ROME
Patent Application for INDUSTRIAL INVENTION

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D. Title: suggested class: **A61K** group/subgroup: **47/30**
Oral solid pharmaceutical formulations with pH-dependent multiphasic release

E. DESIGNED INVENTORS:

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(2) (4)

F. PRIORITY

Country	Type	appl.n No	filing date
1) none			
2)			

G. QUALIFIED CENTRE FOR COLLECTING CULTURES OF MICRO-ORGANISM

H. DIFFERENT NOTES
None

DOCUMENTS ENCLOSED

	N.ex.		
Doc 1)	2	pagg.n. 32	description with abstract and claims
Doc.2)	0	draw.n.	table of drawings
Doc.3)	1		power of attorney, reference declaration to power act
Doc.4)	0		deed of designation of inventor
Doc.5)			priority document with Italian translation
Doc.6)			authorisation or deed of assignment
Doc.7)			complete name of Applicant

8) receipt of payment of Lit. 565.000
Continuous Page – No.

Fill on 14.07.2000 **Sgd. by the Applicant** **The Attorney**
---------- Diego Pallini
Province Office of Industrial Commerce and Craft Milano **Code** 15
Filing certificate **number** MI2000A 001603 **Reg. A**
In the year 2000 **,on the** 14th **day** **of the month** July
The above applicant has submitted to me the undersigned present application for the granting of a Letter Patent above mentioned.
Annotations None
The Depositor **The Ministry officer**

PROSPECTUS A

ABSTRACT OF THE INDUSTRIAL INVENTION WITH MAIN DRAWING, DESCRIPTION AND CLAIM

APPLICATION NUMBER MI2000A 001603 REG. A FILING DATE 14/07/2000

PATENT NUMBER GRANT DATE

A. APPLICANT(S) VALDUCCI Roberto.

RESIDENCE SAVIGNANO SUL RUBICONE (FO)

D. TITLE: ORAL SOLID PHARMACEUTICAL FORMULATIONS WITH PH-DEPENDENT MULTIPHASIC RELEASE

L. ABSTRACT

Oral solid pharmaceutical compositions with pH-dependent multiphasic release, containing, as active principle, a useful molecule in the inflammatory bowel disease therapy, are described, being such compositions suitable to the release of the active principle in the intestinal tract.

M. DRAWING

Description of the industrial invention titled:
"Oral solid pharmaceutical formulations with pH-dependent multiphasic release"
In the name of : Valducci Roberto
Resident in: Savignano sul Rubicone (FO)
Designated inventor: Valducci Roberto MI2000A 001603

* * * * *

INVENTION FIELD

Oral solid pharmaceutical formulations with pH-dependent multiphasic release, containing, as active principle, a molecule useful in the inflammatory bowel disease therapy.

STATE OF THE ART

The ulcerative colitis is a chronic inflammatory form of the colon mucosa; in particular, the inflammatory reaction concerns the large intestine, i.e. the colon with localization in the terminal tract, the rectum and the sigmoid flexure, while the ileum is only seldom involved. In the most serious cases the inflammation can spread to the submucosa.

Crohn's disease or granulomatous colitis is a manifestation of inflammatory type, which usually affects the small intestine, the jejunum and the whole colon, including also the rectum. This inflammatory reaction differs from the ulcerative colitis since, normally, it involves deeper layers of the mucosa.

The differential diagnosis between ulcerative colitis and Crohn's disease is often problematic, so that the international medical literature frequently uses the common term "Inflammatory Bowel Disease" (IBD) to jointly indicate these pathologies.

The therapeutic approach in the various forms of the IBD includes the use of corticosteroids such as prednisone, prednisolone or hydrocortisone, mostly in the acute attacks, together with the administration of liquids, plasma and electrolytes.

For the treatment of the forms from slight-moderate to chronic IBD, in the past, sulfasalazine was commonly used, whose action mechanism is not completely well-known: sulfasalazine, orally administered, reaches unmodified the colon, where it is

transformed by the resident bacteria into sulfapyridine and mesalazine.

Today mesalazine is commonly accepted as the pharmacologically active moiety of sulfasalazine, while sulfapyridine would have just the role of carrier, suitable to carrier the active moiety at the site of action.

Sulfapyridine is not free of toxicity and the intolerance toward such molecule is frequent; therefore, in the last years, much interest has been addressed to the utilization of mesalazine as active principle for the treatment of the forms from slight-moderate to chronic IBD.

The oral administration of mesalazine is made nevertheless problematic by the fact that such drug is almost completely absorbed in the small intestine and, therefore, just a small amount reaches the colon to carry on the therapeutic action. With the purpose of overcoming such difficulty, during the past years, formulations of mesalazine were developed with particular coatings fit to release the active principle only in the desired area, also to avoid systemic side effects. These pharmaceutical compositions are retard, or slow release forms, suitable to prevent or delay the absorption of mesalazine in the proximal tract in order to obtain therapeutic concentrations in the ileum and colon.

The most widespread formulations available on the pharmaceutical market are pH-dependent, time-dependent or bacterium-dependent.

The patent application EP 0 040 590 (in the name of Aktiebolaget Hässle) describes oral pharmaceutical preparations fit to release a drug, for instance mesalazine, selectively in the colon, starting from pH 5.5.

This is obtained through a coating of the active principle with a mixture of an acrylic anionic polymer soluble only at pH 5.5, such as, for example, Eudragit L, in quantities ranging from 10 to 85%, and an acrylic polymer substituted by quaternary ammonium, insoluble in water, like, for example, Eudragit RS or RL, in quantities ranging from 15 to 90%. In these formulations the selective release of the active principle in the intestine is obtained through the utilization of a polymer having a pH-dependent solubility. The blending with one or more polymers having a pH-independent solubility prevents the active principle from being released too rapidly, once reached the solubilization pH.

The patent EP 0 097 651 (in the name of J.B. Tillott Ltd.) regards a solid form of oral dosage, for example a capsule or a tablet, containing a pharmacologically active agent for the treatment of colon pathologies, for instance mesalazine. Such solid form is coated with an anionic polymer, insoluble up to pH 7,

The patent EP 0 572 486 (in the name of J.B. Tillott Ltd.) claims an oral dosage form suitable to dose selectively a drug in the intestine, including a plurality of granules of active principle contained in a capsule. Both the granules and the capsule are coated with equal or different materials, soluble in the intestine, in the ileum or colon, depending on the coating, and this allows a more gradual release of mesalazine in the colon, avoiding, in this way, possible local irritations due to a too fast release. Preferably, the coating of the pharmaceutical forms is composed by polymers that start dissolving at pH $\geq$7.

The patent IT 1246382 (in the name of Eurand International S.p.A.) includes several controlled release oral formulations. In particular, it describes compositions coated with a polymer, for example, Eudragit S, which starts slowly dissolving at pH 6,2, which covers a second polymeric layer suitable to provide a release of the active principle at pH 7,2, for example ethylcellulose. To obtain the desired effect the two membranes have to be applied in a sequence, otherwise, coating the active principle with a mixture of the two components, there is a too quick dissolution of the solid form in the colon.

The patent application EP 0 629 398 (in the name of Tanabe Seiyaku Co. Ltd.) refers to pharmaceutical preparations able to provide a controlled release of the active principle in the desired area of the intestinal tract (duodenum, small intestine, colon, rectum), and anyway at a pH $\geq$5, through a proper choice of the coatings, and checking, furthermore, the dissolution speed of the drug itself. Among the many coatings indicated as useful, Eudragit L and Eudragit S are mentioned.

All the above described formulations have in common the characteristic to start the dissolution of the coating layer at a pH > 5-6, but the real release of the active principle occurs either slowly at a pH higher than 6-6.5, or in a rapid way at a pH higher than 7.

The above mentioned patents are based on the use of a polymer having a solubility

depending on the pH: when the formulation reaches intestinal regions having pH values in which the polymer is soluble, the liberation of mesalazine begins, which can be very rapid or delayed in the case the formulation contains also polymers with a pH-independent solubility. It is nevertheless very difficult with these formulations to obtain the homogeneous distribution of the active principle in the area affected by the inflammatory reaction.

It is therefore necessary to develop new pharmaceutical formulations suitable to assure a uniform release of mesalazine in all the intestinal regions target of the therapeutic action.

SUMMARY OF THE INVENTION

It has been now found out that it is possible to obtain a uniform release of an active principle in all the intestine area hit by IBD by means of pharmaceutical formulations in which polymers or mixtures of different polymers are associated, each one soluble starting from a pH value different from the others and ranging from 6 to 7.

Such pharmaceutical formulations are fit to release active principles in a pH-dependent multiphasic way, that is in more portions with a controlled amount depending on the pH.

DESCRIPTION OF THE INVENTION

The object of the present invention are oral solid formulations containing, as active principle, a molecule useful in the IBD therapy, characterized by the association of different polymers or mixtures of polymers, each one soluble starting from a pH value different from the others and ranging from 6 to 7.

Such formulations release the active principle in a multiphasic way, each phase occurring at a different pH value ranging from 6 to 7.

Particularly preferred is the association of three polymers or mixtures of polymers, soluble starting from a pH value different one from the other and ranging from 6 to 7, which causes a triphasic release of the active principle. Preferred is the combination of a

polymer or a mixture of polymers soluble starting from pH 6, a polymer or a mixture of polymers soluble starting from pH 6,5 and a polymer or a mixture of polymers soluble starting from pH 7, In this case the active principle is released by the invention formulations in a triphasic way, preferably in the following pH-dependent quantities:

pH = 6	10-60% of released active principle
pH = 6.5	10-60% of released active principle
pH = 7	10-60% of released active principle

Even more preferably the active principle release occurs in the following pH-dependent quantities:

pH = 6	30-35% of released active principle
pH = 6.5	30-35% of released active principle
pH = 7	30-35% of released active principle

The invention formulations are particularly suitable to the mesalazine administration. Furthermore, the formulations can be utilized for the administration of other active principles useful in the IBD therapy, among which steroids, such as prednisone, prednisolone or budenoside, antibiotics and anti-inflammatories.

The formulations of this invention can be in the form of capsules containing micro-tablets, tablets, granules or pellets or multilayer tablets. With the term micro-tablet it is identified a tablet having a diameter equal or smaller than 2 mm.

Each capsule contains micro-tablets, tablets, granules or pellets of three types, each one presenting a coating including a polymer soluble starting from a pH value ranging from 6 to 7, such pH value being different for each one of such three types.

Preferably such coating contains from 20 to 100% of said polymer or mixture of polymers. Such coating can include also a fatty acid at 10-20 carbon atoms, preferably stearic acid, usually in a quantity ranging from 0 to 40% and a pharmaceutically acceptable plasticizer, preferably diethylphtalate, usually in a quantity ranging from 0 to 40%.

Preferably in each capsule such three types are contained in proportions suitable to obtain the above described triphasic release profiles; the best ratio is 1:1:1.

According to a particularly preferred application, in each capsule, one third of such micro-tablets, tablets, granules or pellets has a coating including a polymer or a mixture of polymers soluble starting from pH 6, another third includes a coating made of a polymer or a mixture of polymers soluble starting from pH 6,5 and the last third has a coating including a polymer or a mixture of polymers soluble starting from pH 7,

Preferably said polymer soluble starting from pH 6 is Eudragit or cellulose acetatephtalate, said mixture of polymers soluble starting from pH 6,5 is a mixture 1:1 of Eudragit L / Eudragit S, and the polymer soluble starting from pH 7 is Eudragit S.

The above mentioned granules or pellets consist of the active principle and pharmaceutically acceptable excipients, commonly utilized in the preparation of granules and are prepared by means of processes of granulation, nucleation, layering, extrusion and spheronization, that are well-known to the expert of the field.

Said micro-tablets and tablets consist of the active principle and pharmaceutically acceptable excipients commonly used in the preparation of tablets. They can optionally include also from 5 to 35% of a polymer or a mixture of polymers soluble at a pH ranging from 6 to 7, from 0 to 10% of a fatty acid at 12-20 carbon atoms, preferably stearic acid, and from 0 to 10% of a pharmaceutically acceptable plasticizer, preferably diethylphtalate. In this case, the polymer or mixture of polymers contained in the micro-tablets or in the tablets is the same that is included in their coating.

Alternatively, the invention formulation can be in the form of multilayer tablets. These latter are made of three layers, each one including, besides the active principle and the excipients commonly utilized for the preparation of tablets, a polymer or mixture of polymers soluble starting from a pH value ranging from 6 to 7 and different from the pH value at which the polymer or the mixture of polymers of the other two layers dissolves.

Preferably each tablet contains from 5 to 35% of polymer. Optionally, such tablets can contain also a fatty acid at 12-20 carbon atoms, preferably stearic acid, usually in a quantity ranging from 0 to 10% and a pharmaceutically acceptable plasticizer, preferably diethylphtalate, commonly in a quantity ranging from 0 to 10%.

Preferably such layers contain amounts of the active principle suitable to obtain the above described triphasic release profiles; preferably the quantities of active principle in the three layers are equal.

According to a particularly preferred application, the internal layer includes a polymer or a mixture of polymers soluble starting from pH 7, one of the external layer includes a polymer or a mixture of polymers soluble starting from pH 6,5 and the second external layer includes a polymer or a mixture of polymers soluble starting from pH 6, Preferably said polymer soluble starting from pH 6 is Eudragit or cellulose acetatephtalate, saidmixture of polymers soluble starting from pH 6,5 is a mixture 1:1 of Eudragit L / Eudragit S and saidpolymer soluble starting from pH 7 is Eudragit S.

The multilayer tablets present furthermore a coating preferably including a polymer or a mixture of polymers soluble starting from pH 6,5, such as, for instance, a mixture 1:1 of Eudragit S and Eudragit L. Optionally such coating includes also a fatty acid at 12-20 carbon atoms, preferably stearic acid, and/or a plasticizer, preferably diethylphtalate. Preferably such coating contains from 20 to 100% of said mixture of polymers, from 0 to 40% of fatty acid and from 0 to 40% of diethylphtalate.

In case the active principle is mesalazine, the capsules of the present invention contain micro-tablets, granules or pellets for an amount of mesalazine ranging from 100 to 800 mg, as the multilayer tablets contain a mesalazine dosage ranging from 100 to 1500 mg.

EXAMPLE 1

4 Kg of mesalazine have been granulated on a fluid bed with tangential insert. The active principle powder has been sprayed with ethanol or with a mixture 1:1 of water/ethanol containing PVP at 20%. The granules have been selected with a 1200 μm net and the not conform fraction has been micronized, suspended in water/ethanol 1:1 and applied on the granules.

The so obtained granules have been transferred into desiccator and then tested to check the potency and the dissolution rate, obtaining the results reported in Table 1.

The dissolution tests of Table 1 and of the following tables have been carried out with Paddle Apparatus, USP.

Table 1

Mesalazine content	Dissolution (1 hour in HCl 0,1N)	Dissolution (1 hour in tampon pH 6,0)
> 950 mg/g	> 90%	> 90%

EXAMPLE 2

2.1) 500 g of the granulate of the Example 1 have been coated, in two steps, with 600 g of an ethanolic solution containing 7% p/p of Eudragit S, 8.4 g of diethylphtalate and 9 g of stearic acid, using a fluid bed equipped with *bottom spraying* system. For the first coating 400 g of the indicated solution have been utilized; the remaining quantity has been applied in a second coating. After each coating step the granules have been dried and tested. The dissolution tests have provided the results reported in Table 2.

Table 2

Time	Medium	Dissolution % after 1st coating	Dissolution % after 2nd coating
1st hour	HCl 0,1N	n.d.	n.d.
2nd hour		0.71%	4,1%
3rd hour	Tampon pH 6,0	98.7%	4,6%
4th hour	Tampon pH 6,5	--------	7,0%
6th hour	Tampon pH 7,0	--------	97,5%

2.2.) 500 g of product manufactured according to the Example 1 have been coated in a fluid bed with bottom spraying syatem with 600 g of an ethanolic solution containing: 7% p/p of Eudragit L, 8.4 g of diethylphtalate and 9 g of stearic acid. The granules obtained have been dried and tested. The dissolution test has provided the data summarized in Table 3.

Table 3

Time	Medium	Dissolution %

1st hour	HCl 0,1N	3,79%
2nd hour		5,78%
3rd hour	Tampon pH 6,0	91,9%
4th hour	Tampon pH 6,5	-------
6th hour	Tampon pH 7,0	--------

2.3) 500 g of granulate of the Example 1 have been coated with 600 g of a solution containing 7% p/p of a mixture 1:1 of Eudragit L and Eudragit S, 8.4 g of diethylphtalate and 9 g of stearic acid, in a fluid bed equipped with *bottom spraying* syatem. The granules obtained have been dryed and tested, obtaining the results reported in Table 4.

Table 4

Time	Medium	% dissolution
1st hour	HCl 0,1N	0,41%
2nd hour		2,20%
3rd hour	Tampon pH 6,0	17,6%
4th hour	Tampon pH 6,5	98,9%
6th hour	Tampon pH 7,0	-------

2.4) The granules manufactured as described in Examples 2.1, 2.2. and 2.3 have been mixed in the ratio 1:1:1 and inserted into capsules in a quantity corresponding to 400 mg of mesalazine for each capsule. The capsules so obtained have been tested to evaluate the mesalazine dissolution profile. The results obtained are shown in Table 5.

Table 5

Time	Medium	% dissolution
2nd hour	HCl 0,1N	8,20%
3rd hour	Tampon pH 6,0	31,7%
4th hour	Tampon pH 6,5	58,9%
6th hour	Tampon pH 7,0	94,1%

EXAMPLE 3

In a high speed granulator 8 Kg of mesalazine have been wetted with 1.2 Kg of a polyvinylpyrrolidone binder solution at 20% in ethanol and processed to obtain granules having high density and low friability. The granules having granulometry between 500 and 1000 microns have been selected; the granules with a granulometry not included in said range have been micronized, suspended in water / ethanol 1:1 and applied on the fraction of 500 - 1000 microns. The so obtained granules have been divided into three portions and each of these portions has been coated separately in a fluid bed as described in the following example.

EXAMPLE 4

4.1) 2.5 Kg of the granules obtained in the Example 3 have been transferred in a fluid bed and coated with 3.0 Kg of the ethanolic solution of Eudragit S utilized in the Example 2.1. The product obtained has been dried and tested to check the mesalazine release profile. The results obtained in the dissolution test are reported in Table 6.

Table 6

Time	Medium	Dissolution %
1st hour	HCl 0,1N	0,11%
2nd hour		1,50%
3rd hour	Tampon pH 6,0	1,80%
4th hour	Tampon pH 6,5	63,9%
6th hour	Tampon pH 7,0	103,8%

4.2) 2.5 Kg of the granules obtained in the Example 3 have been transferred in a fluid bed and covered with 3.0 Kg of the ethanolic solution of Eudragit L used in the Example 2.2. In Table 7 the results of the dissolution test are reported.

Table 7

Time	Medium	Dissolution %
2nd hour	HCl 0,1N	8,5%
3rd hour	Tampon pH 6,0	74,9%
4th hour	Tampon pH 6,5	96,1%
6th hour	Tampon pH 7,0	100,1%

4.3) 2.5 Kg of the granules obtained in the Example 3 have been transferred in a fluid bed and covered with 3 Kg of the ethanolic solution of Eudragit S and Eudragit L utilized in the Example 2.3. The granules obtained have been dried and tested. In Table 8 the dissolution test results are reported.

Table 8

Time	Medium	Dissolution %
1st hour	HCl 0,1N	0,32%
2nd hour		4,70%
3rd hour	Tampon pH 6,0	21,2%
4th hour	Tampon pH 6,5	97,7%
6th hour	Tampon pH 7,0	98,6%

4.4) The granules coated according to the above Examples 4.1, 4.2 and 4.3 have been mixed in the ratio 1:1:1 and inserted into capsules in a quantity corresponding to 500 mg of mesalazine / capsule. The so obtained capsules have been tested to evaluate the mesalazine release profile. The results obtained in the dissolution test are reported in Table 9.

Table 9

Time	Medium	Dissolution %
2nd hour	HCl 0,1N	6.4%
3rd hour	Tampon pH 6,0	33.2%
4th hour	Tampon pH 6,5	84.5%
6th hour	Tampon pH 7,0	92.3%

EXAMPLE 5

3 Kg of mesalazine have been granulated with 0.8 Kg of a solution at 20% of polyethylene glycol 4000 in ethanol / water 1:2 and the resulting granulate has been extruded and spheronized to obtain granules with an average diameter of 1200 μm. The so obtained granules, coated as described in the examples 4.1, 4.2 and 4.3, have been mixed in the ratio 1:1:1 and inserted into capsules in a quantity corresponding to 500 mg of mesalazine / capsule. The so obtained capsules have provided the dissolution

profile reported in Table 10.

Table 10

Time	Medium	Dissolution %
2nd hour	HCl 0,1N	4,3%
3rd hour	Tampon pH 6,0	30,3%
4th hour	Tampon pH 6,5	80,3%
6th hour	Tampon pH 7,0	93,0%

EXAMPLE 6

The following granulates, suitable for manufacturing tablets, have been prepared by means of a high speed granulator:

6.1) 8 Kg of mesalazine, 1,3 Kg of Eudragit S and 0,3 Kg of stearic acid, micronized, have been granulated adding 1 Kg of an ethanolic solution containing 10% p/p of Eudragit S and 0,03 Kg of diethylphtalate.

6.2) Such granulate has been prepared as described in the Example 6.1, using the following substances and relative quantities:

Mesalazine	8 Kg
Eudragit L	1,3 Kg
Stearic Acid	0,3 Kg
1 Kg of binder solution containing:	
Eudragit L in ethanol	10% p/p
Diethylphtalate	0,03 Kg

6.3) This granulate has been prepared with the same procedure utilized in the Example 6.1, using the following substances and relative quantities:

Mesalazine	8 Kg
Eudragit S	0,65 Kg
Eudragit L	0,65 Kg
Stearic Acid	0,30 Kg
1 Kg of binder solution containing:	
Eudragit S in ethanol	5% p/p

Eudragit L in ethanol	5% p/p
Diethylphtalate	0,03 Kg

EXAMPLE 7

7.1) 1,020 Kg of granulate of the example 6.1 have been mixed with 30 g of magnesium stearate and pressed with round punches having 6 mm of diameter in order to obtain tablets having an average weight of 175 mg. A quantity equal to 950 g of the so obtained tablets has been film-coated in a rotating pan utilizing an ethanolic solution containing 7% p/p of Eudragit S, 2,2% p/p of diethylphtalate and 2% p/p of stearic acid. The film-coating process has been stopped when it has been reached a weight increase of 10 mg per each tablet.

7.2) 1,020 Kg of the granulate of the Example 6.2 have been utilized to prepare tablets as described in Example 7.1, which have been filmed in a rotating pan utilizing 800 g of an ethanolic solution containing 7% p/p Eudragit L, 2,2% of diethylphtalate and 2% of stearic acid. The film-coating process has been protracted up to the achievement of a weight increase of 10 mg per each tablet.

7.3) 1,020 Kg of the granulate of Example 6.3 have been utilized to prepare tablets as described in Example 7.1, which have been then film-coated in a rotating pan utilizing 800 g of an ethanolic solution containing 7% p/p of a mixture 1:1 of Eudragit S and Eudragit L, 2,2% of diethylphtalate and 2% of stearic acid.

7.4) The tablets obtained in the examples 7.1, 7.2 and 7.3 have been inserted into size "0" gelatin capsules in the following quantities:
1 tablet containing Eudragit S (as example 7.1)
1 tablet containing Eudragit L (as example 7.2)
1 tablet containing Eudragit L + S (as example 7.3)

The mesalazine release profile from the so prepared capsules has been analyzed through dissolution tests, obtaining the results reported in Table 11.

Table 11

Time	Medium	Dissolution %
2nd hour	HCl 0,1N	0,5%
3rd hour	Tampon pH 6,0	22,6%
4th hour	Tampon pH 6,5	50,1%
6th hour	Tampon pH 7,0	87,0%

EXAMPLE 8

A new granulate has been prepared putting into a granulator 4.0 Kg of mesalazine wetted with 600 g of a polyvinylpyrrolidone binder solution at 20% in ethanol.

The so obtained granules have been mixed with 80 g of magnesium stearate and pressed to obtain micro-tablets, 2 mm in diameter, and average weight of about 6 mg.

8.1) 500 g of the so obtained micro-tablets have been film-coated in a fluid bed with 600 g of an ethanolic solution containing 7% of Eudragit S, 8,4 g of diethylphtalate and 9 g of stearic acid.

8.2) 500 g of the micro-tablets obtained have been treated as described in the example 8.1 with 600 g of an ethanolic solution containing 7% of Eudragit L, 8,4 g of diethylphtalate and 9 g of stearic acid.

8.3) 500 g of the above obtained tablets have been treated as described in the example 8.1 with 600 g of an ethanolic solution containing 7% of a mixture 1:1 of Eudragit L and Eudragit S, 8,4 g of diethylphtalate and 9 g of stearic acid.

8.4) The tablets obtained as described in the examples 8.1, 8.2 and 8.3 have been mixed between them in the ratio 1:1:1 and inserted into capsules in a quantity equal to 800 mg of mesalazine.
The results obtained by the dissolution test of the so obtained capsules are reported in Table 12.

Table 12

Time	Medium	Dissolution %

2nd hour	HCl 0,1N	6,7%
3rd hour	Tampon pH 6,0	30,8%
4th hour	Tampon pH 6,5	65,1%
6th hour	Tampon pH 7,0	93,3%

EXAMPLE 9

2.5 Kg of mixture of granules and magnesium stearate of the Example 8 have been pressed to obtain tablets with a diameter of 6 mm and an average weight equal to about 140 mg.

9.1) 700 g of such tablets have been coated with the solution described in Example 8.1 up to the obtainment of a weight increase equal to about 13 mg per tablet.

9.2) 700 g of such tablets have been coated with the solution described in Example 8.2 up to the obtainment of a weight increase equal to about 13 mg per tablet.

9.3) 700 g of such tablets have been coated with the solution described in Example 8.3 up to the obtainment of a weight increase equal to about 13 mg per tablet.

9.4) The tablets obtained as described in the examples 9.1, 9.2 and 9.3 have been mixed between them in the ratio 1:1:1 and inserted into capsules in a quantity equal to 400 mg mesalazine.
The results obtained with the dissolution test of the so obtained capsules are reported in Table 13.

Table 13

Time	Medium	Dissolution %
2nd hour	HCl 0,1N	0,2%
3rd hour	Tampon pH 6,0	28,1%
4th hour	Tampon pH 6,5	68,0%
6th hour	Tampon pH 7,0	100%

EXAMPLE 10

The granulates obtained in the examples 6.1, 6.2 and 6.3 have been lubricated with 1% of magnesium stearate and then pressed in the ratio 1:1:1 with oval punches having a length of 18 mm and a width of 8.6 mm, using a three layer tableting machine. The three granulates have been pressed in sequence to obtain tablets having an average weight of about 630 mg. In particular, it has been pressed first the granulate of the Example 6.2, then that of the Example 6.1 and finally that of the Example 6.3. 1 Kg of the so obtained tablets has been then film-coated in a rotating pan with 800 g of an ethanolic solution containing 7% of a mixture 1:1 of Eudragit S and Eudragit L, 11 g of diethylphtalate and 10 g of stearic acid.

The film-coating process of the tablets has been stopped after having reached a weight increase of 45 mg per each tablet.

The results of the dissolution test of the so obtained tablets are reported in Table 14.

Table 14

Time	Medium	Dissolution %
2nd hour	HCl 0,1N	2,7%
3rd hour	Tampon pH 6,0	32,1%
4th hour	Tampon pH 6,5	60,8%
6th hour	Tampon pH 7,0	99,7%

EXAMPLE 11

Clinical evaluation

The clinical evaluation has been carried out administering the formulation of the Example 2.4 in comparison with commercial formulations of mesalazine (Asacol® and Claversal®).

Twelve healthy subjects having an average age of 41,3 years (between 20,2 and 71,4) have been treated, 4 per group, according to the following scheme:

Drug	Active principle per dose	Direction
Asacol® tablets	400 mg	1200 mg die

Claversal® tablets	500 mg	1500 mg die
Formulation of example 2.4	400 mg	1200 mg die

The treatment has lasted 8 days. On the 5th, 6th and 7th day of treatment 7,5 mg of sodium picosulfate have been administered to the patients to facilitate the intestinal washing. The last dose has been administered on the 8th day at 6.00 A.M. The patients have neither eaten nor drunk up to 9.00 A.M., and have been submitted to an intestinal washing through intake of a suitable dose of polyethylene glycol. After each liter of polyethylene glycol solution the patients have taken orally 5 mg of metoclopramide. For the complete intestinal cleaning 3 liters of solution were needed.

The ileoscopy has been carried out between 2.00 P.M. and 3.00 P.M., after sedative analgesia. The biopsies have been carried out according to this order:

- two adjacent samples for the terminal ileum and the caecal ileum valve;
- a sample in the areas indicated in Table 15.

The biopsic fragments have been immediately weighed and frozen in liquid nitrogen, then kept at -80°C. Such procedure has been carried out within 30 minutes from the sample collection. The mesalazine content has been determined in ng/mg of humid weight through HPLC. The results are illustrated in the following Table 15, where the quantity of mesalazine, in ng/mg, detected in each analyzed region, is reported. The Table 15 shows that the formulation object of this invention allows to achieve more homogeneous tissue concentrations of mesalazine than those achieved with the reference formulations, enabling therefore the active principle to perform its activity in the whole anatomical area.

Table 15

Product	ILE	ICV	CAE	ASC	HEP	TRA	SPL	DES	SIG	REC	Average
Asacol®	468,1	551,4	503,7	362,2	230,4	313,3	296,4	121,6	115,2	106,4	306,87
Claversal®	171,5	107,4	97,1	116,4	80,3	123,7	104,6	105,1	80,7	90,7	107,75
Formulation Example 6	321,4	380,3	390,8	360,8	290,4	263,6	220,1	180,6	140,3	110,2	265,85

Legend:

ILE = terminal ileum
ICV = caecal ileum valve
CAE = cecum
ASC = ascending colon
HEP = hepatic flexure
TRA = transverse colon
SPL = splenic flexure
DES = descending colon
SIG = sigmoid colon
REC = rectum

CLAIMS

1. Oral solid formulation containing, as active principle, a substance useful in the IBD therapy, characterized by the association of different polymers or mixtures of polymers, each one soluble starting from a pH value different from the other values and ranging from 6 to 7, and by the multiphasic release of such active principle, each phase occurring at a different pH value ranging from 6 to 7.

2. Formulation according to claim 1 characterized in that said association of polymers or mixtures of polymers consists of three polymers or mixtures of polymers, each one soluble starting from a pH value different from the others two and ranging from 6 to 7 and that said active principle is released in a triphasic way.

3. Formulation according to claim 2 characterized in that said association of polymers or mixtures of polymers consists of a polymer or mixture of polymers soluble starting from pH 6, a polymer or mixture of polymers soluble starting from pH 6,5, and a polymer or mixture of polymers soluble starting from pH 7.

4. Formulation according to claim 3 characterized in that the release of the active principle in every phase occurs in the following pH-dependent ratios:
   pH = 6 10-60% of released active principle
   pH = 6,5 10-60% of released active principle
   pH = 7 10-60% of released active principle

5. Formulation according to claim 4 characterized in that the release of active principle in every phase occurs in the following pH-dependent ratios:
   pH = 6 30-35% of released active principle
   pH = 6,5 30-35% of released active principle
   pH = 7 30-35% of released active principle

6. Formulation according to claim 1 characterized in that said active principle is mesalazine.

7. Formulation according to claim 1 characterized in that said active principle is chosen from the group including steroids, antibiotics and anti-inflammatories.

8. Formulation according to claim 1 in the form of capsule containing micro-tablets, tablets, granules or pellets.

9. Formulation according to claim 8 characterized in that said capsule contains micro-tablets, tablets, granules or pellets of three types, each one having a coating including a polymer soluble starting from a pH value ranging from 6 to 7, said pH value being different for each one of said three types.

10. Formulation according to claim 9 characterized in that the three types are in the ratio 1:1:1.

11. Formulation according to claim 9 characterized in that said coating contains from 20 to 100% of said polymer or mixture of polymers.

12. Formulation according to claim 9 characterized in that said capsule contains one third of such tablets, micro-tablets, granules or pellets having a coating that includes a polymer or a mixture of polymers soluble starting from pH 6, one third having a coating that includes a polymer or a mixture of polymers soluble starting from pH 6,5 and one third having a coating that includes a polymer or a mixture of polymers soluble starting from pH 7.

13. Formulation according to claim 12 characterized in that such polymer soluble starting from pH 6 is chosen from the group including Eudragit L and cellulose acetatephtalate.

14. Formulation according to claim 12 characterized in that such mixture of polymers soluble starting from pH 6,5 is a mixture 1:1 of Eudragit L and Eudragit S.

15. Formulation according to claim 12 characterized in that such polymer soluble starting from pH 7 is Eudragit S.

16. Formulation according to claim 9 characterized in that such coating contains also from 0 to 40% of a fatty acid at 12-20 carbon atoms and from 0 to 40% of a pharmaceutically acceptable plasticizer.

17. Formulation according to claim 16 characterized in that said fatty acid is stearic acid.

18. Formulation according to claim 16 characterized in that said plasticizer is diethylphtalate.

19. Formulation according to claim 9 characterized in that said micro-tablets, tablets, granules or pellets include an active principle and excipients pharmaceutically acceptable.

20. Formulation according to claim 19 characterized in that the micro-tablets and tablets include also from 5 to 35% of the polymer or mixture of polymers contained in their coating, from 0 to 10% of a fatty acid at 12- 20 carbon atoms and from 0 to 10% of a pharmaceutically acceptable plasticizer.

21. Formulation according to claim 20 characterized in that the fatty acid is stearic acid.

22. Formulation according to claim 20 characterized in that said plasticizer is diethylphtalate.

23. Formulation according to claim 1 in the form of a multilayer tablet.

24. Formulation according to claim 23 characterized in that said multilayer tablet is made of three superimposed layers, each one including, besides the active principle and the excipients commonly utilized for the preparation of tablets, a polymer or a mixture of polymers soluble starting from a pH value ranging from 6 to 7 and different from the value at which the polymer or mixture of polymers dissolve in the other two layers.

25. Formulation according to claim 24 characterized in that said three layers contain equal quantities of active principle.

26. Formulation according to claim 24 characterized in that the three layers contain from 5 to 35% of such polymer or mixture of polymers.

27. Formulation according to claim 24 characterized in that, of the three layers, the internal one includes a polymer or mixture of polymers soluble starting from pH 7, one of the external layers includes a polymer or mixture of polymers soluble starting from pH 6,5 and the second external layer includes a polymer or a mixture of polymers soluble starting from pH 6.

28. Formulation according to claim 27 characterized in that said polymer soluble starting from pH 6 is chosen from the group including Eudragit L or cellulose acetatephtalate.

29. Formulation according to claim 27 characterized in that said mixture of polymers soluble starting from pH 6,5 is a mixture 1:1 of Eudragit L / Eudragit S.

30. Formulation according to claim 27 characterized in that the polymer soluble starting from pH 7 is Eudragit S.

31. Formulation according to claim 24 characterized in that said layers include also from 0 to 10% of a fatty acid at 12-20 carbon atoms and from 0 to 10% of a pharmaceutically acceptable plasticizer.

32. Formulation according to claim 31 characterized in that said fatty acid is stearic acid.

33. Formulation according to claim 31 characterized in that said plasticizer is stearic acid.

34. Formulation according to claim 27 characterized in that said multilayer tablets have a coating including a polymer or mixture of polymers soluble at pH 6,5.

35. Formulation according to claim 34 characterized in that said mixture of polymers is a mixture 1:1 of Eudragit S and Eudragit L.

36. Formulation according to claim 34 characterized in that said coating contains from 20 to 100% of such polymer or mixture of polymers.

37. Formulation according to claim 34 characterized in that said coating includes from 0 to 40% of a fatty acid and from 0 to 40% of a pharmaceutically acceptable plasticizer.

38. Formulation according to claim 37 characterized in that said fatty acid is stearic acid.

39. Formulation according to claim 37 characterized in that said plasticizer is diethylphtalate.

40. Formulation according to claim 8 characterized in that includes as active principle from 100 to 800 mg of mesalazine.

41. Formulation according to claim 23 characterized in that includes as active principle, from 100 to 1500 mg of mesalazine.

(MAU/pd)
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